(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 August 2005 (25.08.2005)

PCT

(10) International Publication Number
WO 2005/077373 A2

(51) International Patent Classification[7]: A61K 31/496, A61P 1/04, 1/00, 11/00, 11/06, 43/00

(21) International Application Number: PCT/US2005/000335

(22) International Filing Date: 7 January 2005 (07.01.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/541,055 3 February 2004 (03.02.2004) US

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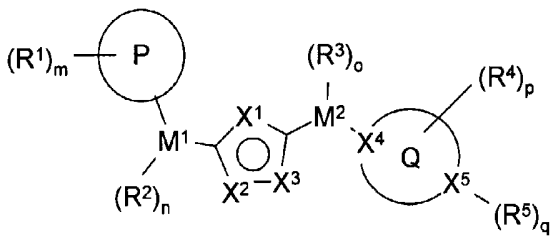
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW TREATMENT OF GERD II



(I)

(57) Abstract: The present invention relates to the use of a compound of formula (I) for the inhibition of transient lower esophageal sphincter relaxations. A further aspect of the invention is directed to the use of compounds of formula I for the treatment of gastro-esophageal reflux disease.

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NEW TREATMENT OF GERD II

Field of the invention

The present invention relates to the use of certain compounds for the inhibition of transient lower esophageal sphincter relaxations. A further aspect of the invention is directed to the use of certain compounds for the treatment of gastro-esophageal reflux disease.

Background of the invention

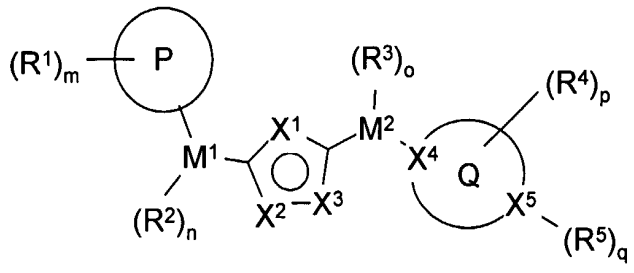
The lower esophageal sphincter (LES) is prone to relaxing intermittently. As a consequence, fluid from the stomach can pass into the esophagus since the mechanical barrier is temporarily lost at such times, an event hereinafter referred to as "reflux".

Gastro-esophageal reflux disease (GERD) is the most prevalent upper gastrointestinal tract disease. Current pharmacotherapy aims at reducing gastric acid secretion, or at neutralizing acid in the esophagus. The major mechanism behind reflux has been considered to depend on a hypotonic lower esophageal sphincter. However, e.g. *Holloway & Dent (1990) Gastroenterol. Clin. N. Amer. 19, pp. 517-535,* has shown that most reflux episodes occur during transient lower esophageal sphincter relaxations (TLESRs), i.e. relaxations not triggered by swallows. It has also been shown that gastric acid secretion usually is normal in patients with GERD.

The object of the present invention was to find a new way for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), thereby preventing reflux. More particularly the object of the invention was to find a new way of treating gastro-esophageal reflux disease (GERD), as well as a new way for the treatment of regurgitation.

Outline of the invention

The present invention is directed to the use of compounds of formula I



(I)

wherein:

P is selected from the group consisting of C_{3-7}alkyl and a 3- to 8-membered ring containing one or more atoms independently selected from C, N, O or S, wherein said ring may be fused with a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S;

R^1 is selected from the group consisting of hydrogen, hydroxy, halo, nitro, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{2-6}alkenyl, OC_{2-6}alkenyl, C_{2-6}alkynyl, OC_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, OC_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, $(CO)R^6$, $O(CO)R^6$, $O(CO)OR^6$, C_{1-6}alkylOR^6, OC_{2-6}alkylOR^6, C_{1-6}alkyl$(CO)R^6$, OC_{1-6}alkyl$(CO)R^6$, C_{0-6}alkylCO_2R^6, OC_{1-6}alkylCO_2R^6, C_{0-6}alkylcyano, OC_{2-6}alkylcyano, C_{0-6}alkylNR^6R^7, OC_{2-6}alkylNR^6R^7, C_{1-6}alkyl$(CO)NR^6R^7$, OC_{1-6}alkyl$(CO)NR^6R^7$, C_{0-6}alkyl$NR^6(CO)R^7$, OC_{2-6}alkyl$NR^6(CO)R^7$, C_{0-6}alkyl$NR^6(CO)NR^6R^7$, C_{0-6}alkylSR^6, OC_{2-6}alkylSR^6, C_{0-6}alkyl$(SO)R^6$, OC_{2-6}alkyl$(SO)R^6$, C_{0-6}alkylSO_2R^6, OC_{2-6}alkylSO_2R^6, C_{0-6}alkyl$(SO_2)NR^6R^7$, OC_{2-6}alkyl$(SO_2)NR^6R^7$, C_{0-6}alkyl$NR^6(SO_2)R^7$, OC_{2-6}alkyl$NR^6(SO_2)R^7$, C_{0-6}alkyl$NR^6(SO_2)NR^6R^7$, OC_{2-6}alkyl$NR^6(SO_2)NR^6R^7$, $(CO)NR^6R^7$, $O(CO)NR^6R^7$, NR^6OR^7, C_{0-6}alkyl$NR^6(CO)OR^7$, OC_{2-6}alkyl$NR^6(CO)OR^7$, SO_3R^6 and a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S, wherein said ring may be substituted by one or more A;

M^1 is selected from the group consisting of a bond, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{0-4}alkyl$(CO)C_{0-4}$alkyl, C_{0-3}alkylOC_{0-3}alkyl, C_{0-3}alkyl$(CO)NR^7R^6$, C_{0-3}alkyl$(CO)NR^7R^6C_{1-3}$alkyl, C_{0-4}alkylNR^7R^6, C_{0-3}alkylSC_{0-3}alkyl, C_{0-3}alkyl$(SO)C_{0-3}$alkyl and C_{0-3}alkyl$(SO_2)C_{0-3}$alkyl;

X^1, X^2 and X^3 are independently selected from the group consisting of CR, CO, N, NR, O and S;

R is selected from the group consisting of hydrogen, C_{0-3}alkyl, halo, C_{0-3}alkylOR^5, C_{0-3}alkylNR^5R^6, C_{0-3}alkyl$(CO)OR^5$, C_{0-3}alkylNR^5R^6 and C_{0-3}alkylaryl;

R^2 is selected from the group consisting of hydrogen, hydroxy, oxo, $=NR^6$, $=NOR^6$, C_{1-4}alkylhalo, halo, C_{1-4}alkyl, OC_{1-4}alkyl, $O(CO)C_{1-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-}

$_4$alkyl(SO_2)C_{0-4}alkyl, (SO)C_{0-4}alkyl, (SO_2)C_{0-4}alkyl, OC_{1-4}alkyl, C_{0-4}alkylcyano, C_{1-4}alkylOR^6 and C_{0-4}alkylNR^6R^7;

M^2 is selected from the group consisting of a bond, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{0-4}alkyl(CO)C_{0-4}alkyl, C_{0-3}alkylOC_{0-3}alkyl, C_{0-3}alkylNR^6C_{1-3}alkyl, C_{0-3}alkyl(CO)NR^6, C_{0-4}alkylNR^6R^7, C_{0-3}alkylSC_{0-3}alkyl, C_{0-3}alkyl(SO)C_{0-3}alkyl and C_{0-3}alkyl(SO_2)C_{0-3}alkyl;

R^3 is selected from the group consisting of hydrogen, hydroxy, oxo, $=NR^6$, $=NOR^6$, C_{1-4}alkylhalo, halo, C_{1-4}alkyl, OC_{1-4}alkyl, O(CO)C_{1-4}alkyl, C_{1-4}alkyl(SO)C_{0-4}alkyl, C_{1-4}alkyl(SO_2)C_{0-4}alkyl, (SO)C_{0-4}alkyl, (SO_2)C_{0-4}alkyl, C_{0-4}alkylcyano, C_{1-4}alkylOR^6 and C_{0-4}alkylNR^6R^7;

X^4 is selected from C, CR or N;

X^5 is selected from C, CR or N;

Q is a 4- to 8-membered ring or bicycle containing one or more atoms independently selected from C, N, O or S, wherein said ring or bicycle may be fused with a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S and wherein the fused ring may be substituted by one or more A;

R^4 is selected from the group consisting of hydrogen, hydroxy, halo, nitro, oxo, C_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, (CO)R^6, O(CO)R^6, C_{1-6}alkylOR^6, OC_{2-6}alkylOR^6, C_{1-6}alkyl(CO)R^6, OC_{1-6}alkyl(CO)R^6, C_{0-6}alkylCO_2R^6, OC_{1-6}alkylCO_2R^6, C_{0-6}alkylcyano, OC_{1-6}alkylcyano, C_{0-6}alkylNR^6R^7, OC_{2-6}alkylNR^6R^7, C_{0-6}alkyl(CO)NR^6R^7, OC_{0-6}alkyl(CO)NR^6R^7, C_{0-6}alkylNR^6(CO)R^7, OC_{2-6}alkylNR^6(CO)R^7, C_{0-6}alkylNR^6(CO)NR^6R^7, C_{0-6}alkylSR^6, OC_{2-6}alkylSR^6, C_{0-6}alkyl(SO)R^6, OC_{2-6}alkyl(SO)R^6, C_{0-6}alkylSO_2R^6, OC_{0-6}alkylSO_2R^6, C_{0-6}alkyl(SO_2)NR^6R^7, OC_{0-6}alkyl(SO_2)NR^6R^7, C_{0-6}alkylNR^6(SO_2)R^7, OC_{2-6}alkylNR^6(SO_2)R^7, NR^6OR^7, NR^6(CO)OR^7, SO_3R^6 and a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S, wherein said ring may be substituted by one or more A;

R^5 is selected from the group consisting of hydrogen, hydroxy, halo, oxo, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, (CO)R^6, O(CO)R^6, O(CO)OR^6, (CO)OR^6, C_{1-6}alkylOR^6, OC_{2-6}alkylOR^6, C_{1-6}alkyl(CO)R^6, OC_{1-6}alkyl(CO)R^6, C_{0-6}alkylCO_2R^6, OC_{1-6}alkylCO_2R^6, C_{0-6}alkylcyano, OC_{0-6}alkylcyano, C_{0-6}alkylNR^6R^7, OC_{2-6}alkylNR^6R^7, C_{1-6}alkyl(CO)NR^6R^7, C_{0-6}alkyl(CO)heteroaryl, C_{0-6}alkyl(CO)aryl, OC_{1-6}alkyl(CO)NR^6R^7, C_{1-6}alkyl(CO)NR^6R^7, C_{0-6}alkylNR^6(CO)R^7, OC_{2-6}alkylNR^6(CO)R^7, C_{0-6}alkylNR^6(CO)NR^6R^7, C_{1-6}alkylNR^6(CO)OR^7 C_{0-6}alkylSR^6, OC_{2-6}alkylSR^6, C_{0-6}alkyl(SO)R^6, OC_{1-6}alkyl(SO)R^6, C_{0-6}alkylSO_2R^6, OC_{0-6}alkylSO_2R^6, C_{0-6}alkyl(SO_2)NR^6R^7, OC_{0-6}alkyl(SO_2)NR^6R^7,C_{0-6}alkylNR^6(SO_2)R^7, OC_{2-6}alkylNR^6(SO_2)R^7,

C_{0-6}alkyl$NR^6(SO_2)NR^6R^7$, OC_{2-6}alkyl$NR^6(SO_2)NR^6R'$, $(CO)NR^6R'$, $O(CO)NR^6R'$, NR^6OR', $NR^6(CO)OR^7$, SO_3R^6 and a 5 -or 6-membered ring containing one or more atoms independently selected from C, N, O or S, wherein said ring may be substituted by one or more A;

R^6 and $R^7$are independently selected from hydrogen, C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{1-6}alkylheteroaryl and a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S, and wherein R^6 and R^7 may together form a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S;

wherein any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl and C_{0-6}alkylheteroaryl defined under R^1, R^2, R^3, R^4, R^5, R^6 and R^7 may be substituted by one or more A;

A is selected from the group consisting of hydroxy, oxo, halo, nitro, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, C_{0-4}alkylC_{3-6}cycloalkyl, C_{2-6}alkenyl, OC_{1-6}alkyl, C_{0-3}alkylaryl, C_{1-6}alkylOR^6, OC_{2-6}alkylOR^6, C_{1-6}alkylSR^6, OC_{2-6}alkylSR^6, $(CO)R^6$, $O(CO)R^6$, OC_{2-6}alkylcyano, C_{0-6}alkylcyano, C_{0-6}alkylCO_2R^6, OC_{1-6}alkylCO_2R^6, $O(CO)OR^6$, OC_{1-6}alkyl$(CO)R^6$, C_{1-6}alkyl$(CO)R^6$, NR^6OR^7, C_{0-6}alkylNR^6R^7, OC_{2-6}alkylNR^6R^7, C_{0-6}alkyl$(CO)NR^6R^7$, OC_{1-6}alkyl$(CO)NR^6R^7$, OC_{2-6}alkyl$NR^6(CO)R^7$, C_{0-6}alkyl$NR^6(CO)R^7$, C_{0-6}alkyl$NR^6(CO)NR^6R^7$, $O(CO)NR^6R^7$, $NR^6(CO)OR^7$, C_{0-6}alkyl$(SO_2)NR^6R^7$, OC_{2-6}alkyl$(SO_2)NR^6R^7$, C_{0-6}alkyl$NR^6(SO_2)R^7$, OC_{2-6}alkyl$NR^6(SO_2)R^7$, SO_3R^6, C_{1-6}alkyl$NR^6(SO_2)NR^6R^7$, OC_{2-6}alkyl$(SO_2)R^6$, C_{0-6}alkyl$(SO_2)R^6$, C_{0-6}alkyl$(SO)R^6$ and OC_{2-6}alkyl$(SO)R^6$;

m and p are independently selected from the group consisting of 0, 1, 2, 3 and 4;

n, o and q are each independently selected from 0, 1, 2 or 3;

or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the inhibition of transient lower esophageal sphincter relaxations (TLESRs).

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-6}' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl,

s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl, t-hexyl. The term "C_{1-3}alkyl" refers to an alkyl group having 1 to 3 carbon atoms, and may be methyl, ethyl, n-propyl or i-propyl.

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring system. The term "C_{3-7}cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl groups. The term "C_{2-6}alkenyl" refers to an alkenyl group having 2 to 6 carbon atoms and one or two double bonds, and may be, but is not limited to vinyl, allyl, propenyl, i-propenyl, butenyl, i-butenyl, crotyl, pentenyl, i-pentenyl or hexenyl.

In this specification, unless stated otherwise, the term "alkynyl" includes both straight and branched chain alkynyl groups. The term "C_{2-6}alkynyl" refres to a group having 2 to 6 carbon atoms and one or two triple bonds, and may be, but is not limited to ethynyl, propargyl, butynyl, i-butynyl, pentynyl, i-pentynyl or hexynyl.

The term "aryl" refers to an optionally substituted monocyclic or bicyclic hydrocarbon ring system containing at least one unsaturated aromatic ring. Examples and suitable values of the term "aryl" are phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indyl and indenyl.

In this specification, unless stated otherwise, the term "heteroaryl" refers to an optionally substituted, unsaturated cyclic hydrocarbon ring system comprising at least one heteroatom and includes, but is not limited to furyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, imidazolyl, imidazolinyl, pyrazolinyl, tetrahydropyranyl.

In this specification, unless stated otherwise, the term "5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S" includes aromatic and heteroaromatic rings as well as carbocyclic and heterocyclic rings which may be saturated or unsaturated. Examples of such rings may be, but are not limited to furyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, thienyl, imidazolyl, imidazolidinyl, imidazolinyl, triazolyl, morpholinyl, piperazinyl, piperidyl, piperidonyl,

pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, thiomorpholinyl, phenyl, cyclohexyl, cyclopentyl or cyclohexenyl.

In this specification, unless stated otherwise, the terms "3- to 8-membered ring containing one or more atoms independently selected from C, N, O or S" includes aromatic and heteroaromatic rings as well as carbocyclic and heterocyclic rings which may be saturated or unsaturated. Examples of such rings may be, but are not limited to imidazolidinyl, imidazolinyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl or thiomorpholinyl, tetrahydrothiopyranyl, furyl, pyrrolyl, isoxazolyl, isothiazolyl, oxazolyl, oxazolidinonyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, thienyl, imidazolyl, triazolyl, phenyl, cyclopropyl, aziridinyl, cyclobutyl, azetidinyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl.

In this specification, unless stated otherwise, the term "3- to 8-membered ring containing one or more atoms independently selected from C, N, O or S, which group may optionally be fused with a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S" includes aromatic and heteroaromatic rings as well as carbocyclic and heterocyclic rings which may be saturated or unsaturated. Examples of such rings may be, but are not limited to naphthyl, norcaryl, chromyl, isochromyl, indanyl, benzoimidazol or tetralinyl, benzooxazolyl, benzothiazolyl, benzofuryl, benzothienyl, benzotriazolyl, indolyl, azaindolyl, indazolyl, indolinyl, isoindolinyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, quinolinyl, quinoxalinyl, benzotriazolyl.

In this specification, unless stated otherwise, the term "$=NR^6$" and "$=NOR^6$" include imino- and oximogroups carrying an R^6 substituent and may be, or be part of, groups including, but not limited to iminoalkyl, iminohydroxy, iminoalkoxy, amidine, hydroxyamidine, alkoxyamidine.

In the case where a subscript is the integer 0 (zero) the group to which the subscript refers to indicates that the group is absent, i.e. there is a direct bond between the groups.

In this specification, unless stated otherwise, the term "bond" may be a saturated or unsaturated bond.

In this specification, unless stated otherwise, the term "halo" may be fluoro, chloro, bromo or iodo.

In this specification, unless stated otherwise, the term "alkylhalo" means an alkyl group as defined above, which is substituted with one or more halo. The term "C_{1-6}alkylhalo" may include, but is not limited to fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, bromopropyl. The term "OC_{1-6}alkylhalo" may include, but is not limited to fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy, difluoroethoxy.

Specific examples of compounds useful according to the present invention include
4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester hydrochloride,
4-[5-(3-Methoxyphenyl)-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester hydrochloride,
4-[5-(3-Trifluoromethyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(3-Cyano-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester),
4-[5-(3-Fluoro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(3-Iodo-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(3-Trifluoromethoxy-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(3-Bromo-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid methyl ester,
4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid propyl ester,
4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid butyl ester,
4-[5-(3-Methoxy-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-2-methyl-piperazine-1-carboxylic acid ethyl ester,
4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid isopropyl ester,
4-[1-(5-(3-Methyl-phenyl)-[1,2,4]oxadiazol-3-yl)-ethyl]-piperazine-carboxylic acid ethyl ester or
4-[5-(3-Furan-3-yl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-{Cyano-[5-(2-fluoro-5-methyl-phenyl)-isoxazol-3-yl]-methyl}-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-2-oxo-piperazine-1-carboxylic acid ethyl ester,

4-[1-(5-m-Tolyl-[1,2,4]oxadiazol-3-yl)-ethyl]-piperazine-1-carboxylic acid ethyl-methyl-amide,

(R)-and (S)-4-[1-(5-(3-Methyl-phenyl)-[1,2,4]oxadiazol-3-yl)-ethyl]-piperazine-carboxylic acid ethyl ester,

(R)-and (S)-4-[1-(5-(3-Methyl-phenyl)-[1,2,4]oxadiazol-3-yl)-ethyl]-piperazine-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-propyl}-piperazine-1-carboxylic acid ethyl ester,

(S)-4-{1-[5-(5-Chloro-2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

(S)-{1-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

(S)-4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

(R)-4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-2-methyl-piperazine-1-carboxylic acid ethyl ester,

(S)- 4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-2-methyl-piperazine-1-carboxylic acid ethyl ester,

(R)-3-Methyl-4-(5-m-tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester,

(S)-3-Methyl-4-(5-m-tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Methylsulfanyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Chloro-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-yl-(R)-methyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-yl-(S)-methyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Bromo-2-fluoro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2,5-Dichloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-(5-Thiophen-3-yl-isoxazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester,
4-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester, 4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,
(R)- and (S)-4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester enantiomers,
4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-propyl}-piperazine-1-carboxylic acid ethyl ester,
4-{Cyclopropyl-[5-(2-fluoro-5-methyl-phenyl)-isoxazol-3-yl]-methyl}-piperazine-1-carboxylic acid ethyl ester,
4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-ethyl}-3-(*R*)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)
4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-ethyl}-3-(*S*)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)
4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-3-(*R*)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)
4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-3-(*S*)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)
4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-2-(R)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)
4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-2-(S)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)
(*R*)-4-[5-(3-Chloro-phenyl)-isoxazol-3-ylmethyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,
(*R*)-4-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-ylmethyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,
(*S*)-4-[5-(3-Chloro-phenyl)-isoxazol-3-ylmethyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,
(*S*)-4-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-ylmethyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,
4-[5-(3-Chloro-phenyl)-oxazol-2-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(5-Chloro-2-fluoro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(2-Chloro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-3-(*S*)-methyl-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-3-(*R*)-methyl-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-3-(*R*)-methyl-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Chloro-2-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(5-Chloro-2-fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(2-Fluoro-5-methyl-phenyl)-[1,3,4]oxadiazol-2-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-(5-m-Tolyl-isoxazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-methoxy-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-cyano-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Formyl-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Cyano-2-fluoro-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Chloro-2-fluoro-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(5-Chloro-2-fluoro-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-[1-(5-m-Tolyl-isoxazol-3-yl)-ethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Methoxy-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Cyano-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(5-Cyano-2-fluoro-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(2-Methyl-pyridin-4-yl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(5-Chloro-2-fluoro-phenyl)-isoxazol-3-yl]-2,2,2-trifluoro-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-iodo-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Hydroxy-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Chloro-2-hydroxy-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

or a salt thereof.

The compounds of formula I useful in accordance with the present invention, may also be used as pharmaceutically acceptable salts, but also other salts may be useful in accordance with the present invention.

Examples of pharmaceutically acceptable salts useful in accordance with the present invention are, but are not limited to, hydrochloride, 4-aminobenzoate, anthranilate, 4-aminosalicylate, 4-hydroxybenzoate, 3,4-dihydroxybenzoate, 3-hydroxy-2-naphthoate, nitrate and trifluoroacetate.

Some compounds of formula I may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses the use of all such optical, diastereoisomers and geometric isomers.

The invention also relates to the use of any and all tautomeric forms of the compounds of formula I.

A further aspect of the invention is the use of a compound formula I for the manufacture of a medicament for the prevention of reflux.

Still a further aspect of the invention is the use of a compound of formula I for the manufacture of a medicament for the treatment of gastro-esophageal reflux disease (GERD).

Effective prevention of regurgitation would be an important way of preventing, as well as curing lung disease due to aspiration of regurgitated gastric contents, and for managing failure to thrive. Thus, a further aspect of the invention is the use of a compound of formula I for the manufacture of a medicament for the treatment of regurgitation.

Still a further aspect of the invention is the use of a compound of formula I for the manufacture of a medicament for the treatment or prevention of lung disease.

Another aspect of the invention is the use of a compound of formula I for the manufacture of a medicament for the management of failure to thrive.

Still a further aspect of the invention is the use of a compound of formula I for the manufacture of a medicament for the treatment or prevention of asthma, such as reflux-related asthma.

Another aspect of the invention is the use of a compound of formula I for the manufacture of a medicament for the treatment or prevention of chronic laryngitis.

A further aspect of the invention is the use of a compound according to formula I for the manufacture of a medicament for the treatment or prevention of functional gastrointestinal disorders, such as functional dyspepsia (FD). Yet another aspect of the invention is the use of a compound according to formula I for the manufacture of a medicament for the treatment or prevention of irritable bowel syndrome (IBS), such as constipation predominant IBS, diarrhea predominant IBS or alternating bowel movement predominant IBS.

A further aspect of the present invention is a method for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I is administered to a subject in need of such inhibition.

Another aspect of the invention is a method for the prevention of reflux, whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I is administered to a subject in need of such prevention.

Still a further aspect of the invention is a method for the treatment of gastro-esophageal reflux disease (GERD), whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I is administered to a subject in need of such treatment.

Yet another aspect of the invention is a method for the treatment of regurgitation, whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I is administered to a subject in need of such treatment.

Still a further aspect of the invention is a method for the treatment or prevention of asthma, such as reflux-related asthma, whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I is administered to a subject in need of such treatment.

Yet another aspect of the invention is a method for the treatment of chronic laryngitis, whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I is administered to a subject in need of such treatment.

Still a further aspect of the invention is a method for the treatment or inhibition of lung disease, whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I is administered to a subject in need of such treatment.

Still a further aspect of the invention is a method for the management of failure to thrive, whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I is administered to a subject in need of such treatment.

The wording "TLESR", transient lower esophageal sphincter relaxations, is herein defined in accordance with *Mittal, R.K., Holloway, R.H., Penagini, R., Blackshaw, L.A., Dent, J., 1995; Transient lower esophageal sphincter relaxation. Gastroenterology 109, pp. 601-610.*

The wording "reflux" is defined as fluid from the stomach being able to pass into the esophagus, since the mechanical barrier is temporarily lost at such times.

The wording "GERD", gastro-esophageal reflux disease, is defined in accordance with *van Heerwarden, M.A., Smout A.J.P.M., 2000; Diagnosis of reflux disease. Baillière's Clin. Gastroenterol. 14, pp. 759-774.*

Pharmaceutical formulations

For clinical use, the compounds of formula I are in accordance with the present invention suitably formulated into pharmaceutical formulations for oral administration. Also rectal, parenteral or any other route of administration may be contemplated to the skilled man in the art of formulations. Thus, the compounds of formula I are formulated with at least one pharmaceutically and pharmacologically acceptable carrier or adjuvant. The carrier may be in the form of a solid, semi-solid or liquid diluent.

In the preparation of oral pharmaceutical formulations in accordance with the invention, the compound of formula I to be formulated is mixed with solid, powdered ingredients such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or compressed into tablets.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Hard gelatine capsules may contain the active compound in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance(s) mixed with a neutral fat base; (ii) in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil, or other suitable vehicle for gelatine rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions, containing the active compound and the remainder of the formulation consisting of sugar or sugar alcohols, and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain

colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent. These solutions may also contain stabilizing ingredients and/or buffering ingredients and are dispensed into unit doses in the form of ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

In one aspect of the present invention, the compound of formula I may be administered once or twice daily, depending on the severity of the patient's condition.

Methods of Preparation

The compounds of formula I can be prepared as described in WO2004/014370 A2.

Biological evaluation

Screening for compounds active against TLESR

Adult Labrador retrievers of both genders, trained to stand in a Pavlov sling, are used. Mucosa-to-skin esophagostomies are formed and the dogs are allowed to recover completely before any experiments are done.

Motility measurement

In brief, after fasting for approximately 17 h with free supply of water, a multilumen sleeve/sidehole assembly (Dentsleeve, Adelaide, South Australia) is introduced through the esophagostomy to measure gastric, lower esophageal sphincter (LES) and esophageal pressures. The assembly is perfused with water using a low-compliance manometric perfusion pump (Dentsleeve, Adelaide, South Australia). An air-perfused tube is passed in the oral direction to

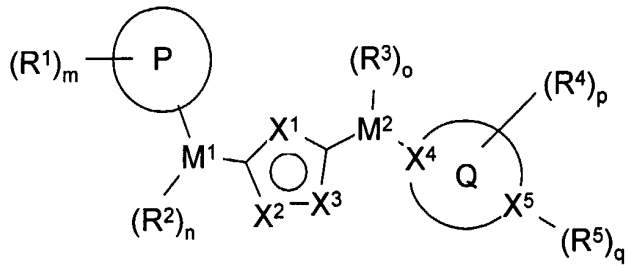
measure swallows, and an antimony electrode monitored pH, 3 cm above the LES. All signals are amplified and acquired on a personal computer at 10 Hz.

When a baseline measurement free from fasting gastric/LES phase III motor activity has been obtained, placebo (0.9% NaCl) or test compound is administered intravenously (i.v., 0.5 ml/kg) in a foreleg vein. Ten min after i.v. administration, a nutrient meal (10% peptone, 5% D-glucose, 5% Intralipid, pH 3.0) is infused into the stomach through the central lumen of the assembly at 100 ml/min to a final volume of 30 ml/kg. Immediately following the meal, air is insufflated at 40 ml/min. In an alternative model (Barostat model), the infusion of the nutrient meal is followed by air infusion at a rate of 500 ml/min until a intragastric pressure of 10±1 mmHg is obtained. The pressure is then maintained at this level throughout the experiment using the infusion pump for further air infusion or for venting air from the stomach. The experimental time from start of nutrient infusion to end of air insufflation is 45 min. The procedure has been validated as a reliable means of triggering TLESRs.

TLESRs is defined as a decrease in lower esophageal sphincter pressure (with reference to intragastric pressure) at a rate of >1 mmHg/s. The relaxation should not be preceded by a pharyngeal signal $\leq$2s before its onset in which case the relaxation is classified as swallow-induced. The pressure difference between the LES and the stomach should be less than 2 mmHg, and the duration of the complete relaxation longer than 1 s.

Claims

1. Use of a compound formula I



(I)

(I)

wherein:

P is selected from the group consisting of C_{3-7}alkyl and a 3- to 8-membered ring containing one or more atoms independently selected from C, N, O or S, wherein said ring may be fused with a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S;

R^1 is selected from the group consisting of hydroxy, halo, nitro, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{2-6}alkenyl, OC_{2-6}alkenyl, C_{2-6}alkynyl, OC_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, OC_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, $(CO)R^6$, $O(CO)R^6$, $O(CO)OR^6$, C_{1-6}alkylOR^6, OC_{2-6}alkylOR^6, C_{1-6}alkyl$(CO)R^6$, OC_{1-6}alkyl$(CO)R^6$, C_{0-6}alkylCO_2R^6, OC_{1-6}alkylCO_2R^6, C_{0-6}alkylcyano, OC_{2-6}alkylcyano, C_{0-6}alkylNR^6R^7, OC_{2-6}alkylNR^6R^7, C_{1-6}alkyl$(CO)NR^6R^7$, OC_{1-6}alkyl$(CO)NR^6R^7$, C_{0-6}alkyl$NR^6(CO)R^7$, OC_{2-6}alkyl$NR^6(CO)R^7$, C_{0-6}alkyl$NR^6(CO)NR^6R^7$, C_{0-6}alkylSR^6, OC_{2-6}alkylSR^6, C_{0-6}alkyl$(SO)R^6$, OC_{2-6}alkyl$(SO)R^6$, C_{0-6}alkylSO_2R^6, OC_{2-6}alkylSO_2R^6, C_{0-6}alkyl$(SO_2)NR^6R^7$, OC_{2-6}alkyl$(SO_2)NR^6R^7$, C_{0-6}alkyl$NR^6(SO_2)R^7$, OC_{2-6}alkyl$NR^6(SO_2)R^7$, C_{0-6}alkyl$NR^6(SO_2)NR^6R^7$, OC_{2-6}alkyl$NR^6(SO_2)NR^6R^7$, $(CO)NR^6R^7$, $O(CO)NR^6R^7$, NR^6OR^7, C_{0-6}alkyl$NR^6(CO)OR^7$, OC_{2-6}alkyl$NR^6(CO)OR^7$, SO_3R^6 and a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S, wherein said ring may be substituted by one or more A;

M^1 is selected from the group consisting of a bond, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{0-4}alkyl$(CO)C_{0-4}$alkyl, C_{0-3}alkylOC_{0-3}alkyl, C_{0-3}alkyl$(CO)NR^7R^6$, C_{0-3}alkyl$(CO)NR^7R^6C_{1-3}$alkyl, C_{0-4}alkylNR^7R^6, C_{0-3}alkylSC_{0-3}alkyl, C_{0-3}alkyl$(SO)C_{0-3}$alkyl and C_{0-3}alkyl$(SO_2)C_{0-3}$alkyl;

X^1, X^2 and X^3 are independently selected from the group consisting of CR, CO, N, NR, O and S;

R is selected from the group consisting of hydrogen, C_{0-3}alkyl, halo, C_{0-3}alkylOR^5, C_{0-3}alkylNR^5R^6, C_{0-3}alkyl$(CO)OR^5$, C_{0-3}alkylNR^5R^6 and C_{0-3}alkylaryl;

R^2 is selected from the group consisting of hydrogen, hydroxy, oxo, $=NR^6$, $=NOR^6$, C_{1-4}alkylhalo, halo, C_{1-4}alkyl, OC_{1-4}alkyl, $O(CO)C_{1-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-4}alkyl$(SO_2)C_{0-4}$alkyl, $(SO)C_{0-4}$alkyl, $(SO_2)C_{0-4}$alkyl, OC_{1-4}alkyl, C_{0-4}alkylcyano, C_{1-4}alkylOR^6 and C_{0-4}alkylNR^6R^7;

M^2 is selected from the group consisting of a bond, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{0-4}alkyl$(CO)C_{0-4}$alkyl, C_{0-3}alkylOC_{0-3}alkyl, C_{0-3}alkylNR^6C_{1-3}alkyl, C_{0-3}alkyl$(CO)NR^6$, C_{0-4}alkylNR^6R^7, C_{0-3}alkylSC_{0-3}alkyl, C_{0-3}alkyl$(SO)C_{0-3}$alkyl and C_{0-3}alkyl$(SO_2)C_{0-3}$alkyl;

R^3 is selected from the group consisting of hydrogen, hydroxy, oxo, $=NR^6$, $=NOR^6$, C_{1-4}alkylhalo, halo, C_{1-4}alkyl, OC_{1-4}alkyl, $O(CO)C_{1-4}$alkyl, C_{1-4}alkyl$(SO)C_{0-4}$alkyl, C_{1-4}alkyl$(SO_2)C_{0-4}$alkyl, $(SO)C_{0-4}$alkyl, $(SO_2)C_{0-4}$alkyl, C_{0-4}alkylcyano, C_{1-4}alkylOR^6 and C_{0-4}alkylNR^6R^7;

X^4 is selected from C, CR or N;

X^5 is selected from C, CR or N;

Q is a 4- to 8-membered ring or bicycle containing one or more atoms independently selected from C, N, O or S, wherein said ring or bicycle may be fused with a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S and wherein the fused ring may be substituted by one or more A;

R^4 is selected from the group consisting of hydrogen, hydroxy, halo, nitro, oxo, C_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, $(CO)R^6$, $O(CO)R^6$, C_{1-6}alkylOR^6, OC_{2-6}alkylOR^6, C_{1-6}alkyl$(CO)R^6$, OC_{1-6}alkyl$(CO)R^6$, C_{0-6}alkylCO_2R^6, OC_{1-6}alkylCO_2R^6, C_{0-6}alkylcyano, OC_{1-6}alkylcyano, C_{0-6}alkylNR^6R^7, OC_{2-6}alkylNR^6R^7, C_{0-6}alkyl$(CO)NR^6R^7$, OC_{0-6}alkyl$(CO)NR^6R^7$, C_{0-6}alkyl$NR^6(CO)R^7$, OC_{2-6}alkyl$NR^6(CO)R^7$, C_{0-6}alkyl$NR^6(CO)NR^6R^7$, C_{0-6}alkylSR^6, OC_{2-6}alkylSR^6, C_{0-6}alkyl$(SO)R^6$, OC_{2-6}alkyl$(SO)R^6$, C_{0-6}alkylSO_2R^6, OC_{0-6}alkylSO_2R^6, C_{0-6}alkyl$(SO_2)NR^6R^7$, OC_{0-6}alkyl$(SO_2)NR^6R^7$, C_{0-6}alkyl$NR^6(SO_2)R^7$, OC_{2-6}alkyl$NR^6(SO_2)R^7$, NR^6OR^7, $NR^6(CO)OR^7$, SO_3R^6 and a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S, wherein said ring may be substituted by one or more A;

R^5 is selected from the group consisting of hydrogen, hydroxy, halo, oxo, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, $(CO)R^6$, $O(CO)R^6$, $O(CO)OR^6$, $(CO)OR^6$, C_{1-6}alkylOR^6, OC_{2-6}alkylOR^6, C_{1-6}alkyl$(CO)R^6$, OC_{1-6}alkyl$(CO)R^6$, C_{0-6}alkylCO_2R^6, OC_{1-6}alkylCO_2R^6, C_{0-6}alkylcyano, OC_{0-6}alkylcyano, C_{0-6}alkylNR^6R^7, OC_{2-6}alkylNR^6R^7, C_{1-6}alkyl$(CO)NR^6R^7$, C_{0-

$_{6}$alkyl(CO)heteroaryl, C_{0-6}alkyl(CO)aryl, OC_{1-6}alkyl(CO)NR^6R^7, C_{1-6}alkyl(CO)NR^6R^7, C_{0-6}alkyl$NR^6(CO)R^7$, OC_{2-6}alkyl$NR^6(CO)R^7$, C_{0-6}alkyl$NR^6(CO)NR^6R^7$, C_{1-6}alkyl$NR^6(CO)OR^7$ C_{0-6}alkylSR^6, OC_{2-6}alkylSR^6, C_{0-6}alkyl(SO)R^6, OC_{1-6}alkyl(SO)R^6, C_{0-6}alkylSO_2R^6, OC_{0-6}alkylSO_2R^6, C_{0-6}alkyl(SO_2)NR^6R^7, OC_{0-6}alkyl(SO_2)NR^6R^7,C_{0-6}alkyl$NR^6(SO_2)R^7$, OC_{2-6}alkyl$NR^6(SO_2)R^7$, C_{0-6}alkyl$NR^6(SO_2)NR^6R^7$, OC_{2-6}alkyl$NR^6(SO_2)NR^6R^7$, (CO)NR^6R^7, O(CO)NR^6R^7, NR^6OR^7, $NR^6(CO)OR^7$, SO_3R^6 and a 5 -or 6-membered ring containing one or more atoms independently selected from C, N, O or S, wherein said ring may be substituted by one or more A;

R^6 and $R^7$are independently selected from hydrogen, C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{1-6}alkylheteroaryl and a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S, and wherein R^6 and R^7 may together form a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S;

wherein any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl and C_{0-6}alkylheteroaryl defined under R^1, R^2, R^3, R^4, R^5, R^6 and R^7 may be substituted by one or more A;

A is selected from the group consisting of hydrogen, hydroxy, oxo, halo, nitro, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, C_{0-4}alkylC_{3-6}cycloalkyl, C_{2-6}alkenyl, OC_{1-6}alkyl, C_{0-3}alkylaryl, C_{1-6}alkylOR^6, OC_{2-6}alkylOR^6, C_{1-6}alkylSR^6, OC_{2-6}alkylSR^6, (CO)R^6, O(CO)R^6, OC_{2-6}alkylcyano, C_{0-6}alkylcyano, C_{0-6}alkylCO_2R^6, OC_{1-6}alkylCO_2R^6, O(CO)OR^6, OC_{1-6}alkyl(CO)R^6, C_{1-6}alkyl(CO)R^6, NR^6OR^7, C_{0-6}alkylNR^6R^7, OC_{2-6}alkylNR^6R^7, C_{0-6}alkyl(CO)NR^6R^7, OC_{1-6}alkyl(CO)NR^6R^7, OC_{2-6}alkyl$NR^6(CO)R^7$, C_{0-6}alkyl$NR^6(CO)R^7$, C_{0-6}alkyl$NR^6(CO)NR^6R^7$, O(CO)NR^6R^7, $NR^6(CO)OR^7$, C_{0-6}alkyl(SO_2)NR^6R^7, OC_{2-6}alkyl(SO_2)NR^6R^7, C_{0-6}alkyl$NR^6(SO_2)R^7$, OC_{2-6}alkyl$NR^6(SO_2)R^7$, SO_3R^6, C_{1-6}alkyl$NR^6(SO_2)NR^6R^7$, OC_{2-6}alkyl(SO_2)R^6, C_{0-6}alkyl(SO_2)R^6, C_{0-6}alkyl(SO)R^6 and OC_{2-6}alkyl(SO)R^6;

m and p are independently selected from the group consisting of 0, 1, 2, 3 and 4;

n, o and q are each independently selected from 0, 1, 2 or 3;

or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the inhibition of transient lower esophageal sphincter relaxations (TLESRs).

2. Use of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the treatment of gastro-esophageal reflux disease (GERD).

3. Use of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the prevention of reflux.

4. Use of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the treatment of, or prevention of, regurgitation.

5. Use of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the treatment of, or prevention of, asthma.

6. Use according to claim 5, wherein the asthma is reflux-related asthma.

7. Use of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the treatment of, or prevention of, laryngitis.

8. Use of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for the treatment of, or prevention of, lung disease.

9. Use of a compound of formula I as defined in claim 1, or a pharmaceutically acceptable salt or an optical isomer thereof, for the manufacture of a medicament for managing failure to thrive.

10. Use according to any one of the preceding claims, wherein the compound of formula I is selected from the group of compounds consisting of 4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester hydrochloride,

4-[5-(3-Methoxyphenyl)-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester hydrochloride,

4-[5-(3-Trifluoromethyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Cyano-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester),

4-[5-(3-Fluoro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Iodo-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Trifluoromethoxy-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Bromo-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid methyl ester,

4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid propyl ester,

4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid butyl ester,

4-[5-(3-Methoxy-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-2-methyl-piperazine-1-carboxylic acid ethyl ester,

4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid isopropyl ester,

4-[1-(5-(3-Methyl-phenyl)-[1,2,4]oxadiazol-3-yl)-ethyl]-piperazine-carboxylic acid ethyl ester or

4-[5-(3-Furan-3-yl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{Cyano-[5-(2-fluoro-5-methyl-phenyl)-isoxazol-3-yl]-methyl}-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-2-oxo-piperazine-1-carboxylic acid ethyl ester,

4-[1-(5-m-Tolyl-[1,2,4]oxadiazol-3-yl)-ethyl]-piperazine-1-carboxylic acid ethyl-methyl-amide,

(R)-and (S)-4-[1-(5-(3-Methyl-phenyl)-[1,2,4]oxadiazol-3-yl)-ethyl]-piperazine-carboxylic acid ethyl ester,

(R)-and (S)-4-[1-(5-(3-Methyl-phenyl)-[1,2,4]oxadiazol-3-yl)-ethyl]-piperazine-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-propyl}-piperazine-1-carboxylic acid ethyl ester,

(S)-4-{1-[5-(5-Chloro-2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

(S)-{1-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

(S)-4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

(R)-4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-2-methyl-piperazine-1-carboxylic acid ethyl ester,

(S)- 4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-2-methyl-piperazine-1-carboxylic acid ethyl ester,

(R)-3-Methyl-4-(5-m-tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester,

(S)-3-Methyl-4-(5-m-tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester, 4-[5-(3-Methylsulfanyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Chloro-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-yl-(R)-methyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-yl-(S)-methyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Bromo-2-fluoro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2,5-Dichloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-(5-Thiophen-3-yl-isoxazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,
4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,
(R)- and (S)-4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester enantiomers,
4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-propyl}-piperazine-1-carboxylic acid ethyl ester,
4-{Cyclopropyl-[5-(2-fluoro-5-methyl-phenyl)-isoxazol-3-yl]-methyl}-piperazine-1-carboxylic acid ethyl ester,
4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-ethyl}-3-(*R*)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)
4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-ethyl}-3-(*S*)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)
4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-3-(*R*)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)
4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-3-(*S*)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)
4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-2-(R)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)
4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-2-(S)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)
(*R*)-4-[5-(3-Chloro-phenyl)-isoxazol-3-ylmethyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,
(*R*)-4-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-ylmethyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,
(*S*)-4-[5-(3-Chloro-phenyl)-isoxazol-3-ylmethyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,
(*S*)-4-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-ylmethyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,
4-[5-(3-Chloro-phenyl)-oxazol-2-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(5-Chloro-2-fluoro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(2-Chloro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-3-(*S*)-methyl-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-3-(*R*)-methyl-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-3-(*R*)-methyl-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Chloro-2-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(5-Chloro-2-fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(2-Fluoro-5-methyl-phenyl)-[1,3,4]oxadiazol-2-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-(5-m-Tolyl-isoxazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-methoxy-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-cyano-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Formyl-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Cyano-2-fluoro-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Chloro-2-fluoro-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(5-Chloro-2-fluoro-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-[1-(5-m-Tolyl-isoxazol-3-yl)-ethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Methoxy-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Cyano-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(5-Cyano-2-fluoro-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(2-Methyl-pyridin-4-yl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(5-Chloro-2-fluoro-phenyl)-isoxazol-3-yl]-2,2,2-trifluoro-ethyl}-piperazine-1-carboxylic acid ethyl ester,

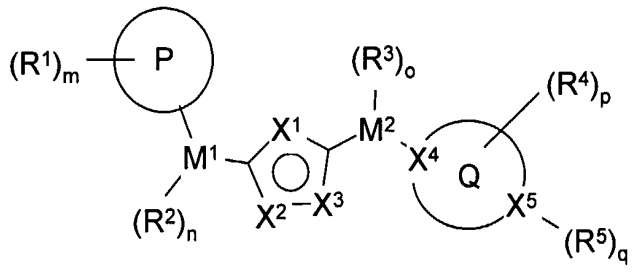
4-[5-(2-Fluoro-5-iodo-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Hydroxy-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Chloro-2-hydroxy-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

or a pharmaceutically acceptable salt or an optical isomer thereof.

11. A method for the inhibition of transient lower esophageal sphincter relaxations (TLESRs), whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I



(I)

(I)

wherein:

P is selected from the group consisting of C_{3-7}alkyl and a 3- to 8-membered ring containing one or more atoms independently selected from C, N, O or S, wherein said ring may be fused with a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S;

R^1 is selected from the group consisting of hydrogen, hydroxy, halo, nitro, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{2-6}alkenyl, OC_{2-6}alkenyl, C_{2-6}alkynyl, OC_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, OC_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, $(CO)R^6$, $O(CO)R^6$, $O(CO)OR^6$, C_{1-6}alkylOR^6, OC_{2-6}alkylOR^6, C_{1-6}alkyl$(CO)R^6$, OC_{1-6}alkyl$(CO)R^6$, C_{0-6}alkylCO_2R^6, OC_{1-6}alkylCO_2R^6, C_{0-6}alkylcyano, OC_{2-6}alkylcyano, C_{0-6}alkylNR^6R^7, OC_{2-6}alkylNR^6R^7, C_{1-6}alkyl$(CO)NR^6R^7$, OC_{1-6}alkyl$(CO)NR^6R^7$, C_{0-6}alkyl$NR^6(CO)R^7$, OC_{2-6}alkyl$NR^6(CO)R^7$, C_{0-6}alkyl$NR^6(CO)NR^6R^7$, C_{0-6}alkylSR^6, OC_{2-6}alkylSR^6, C_{0-6}alkyl$(SO)R^6$, OC_{2-6}alkyl$(SO)R^6$, C_{0-6}alkylSO_2R^6, OC_{2-6}alkylSO_2R^6, C_{0-6}alkyl$(SO_2)NR^6R^7$, OC_{2-6}alkyl$(SO_2)NR^6R^7$, C_{0-6}alkyl$NR^6(SO_2)R^7$, OC_{2-6}alkyl$NR^6(SO_2)R^7$,

C_{0-6}alkylNR^6(SO$_2$)NR^{6}R^7, OC$_{2-6}$alkylNR^6(SO$_2$)NR^{6}R^7, (CO)NR^{6}R^7, O(CO)NR^{6}R^7, NR^{6}OR^7, C_{0-6}alkylNR^6(CO)OR^7, OC$_{2-6}$alkylNR^6(CO)OR^7, SO$_3$R^6 and a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S, wherein said ring may be substituted by one or more A;

M^1 is selected from the group consisting of a bond, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{0-4}alkyl(CO)C_{0-4}alkyl, C_{0-3}alkylOC$_{0-3}$alkyl, C_{0-3}alkyl(CO)NR^{7}R^6, C_{0-3}alkyl(CO)NR^{7}R^{6}C$_{1-3}$alkyl, C_{0-4}alkylNR^{7}R^6, C_{0-3}alkylSC$_{0-3}$alkyl, C_{0-3}alkyl(SO)C_{0-3}alkyl and C_{0-3}alkyl(SO$_2$)C$_{0-3}$alkyl;

X^1, X^2 and X^3 are independently selected from the group consisting of CR, CO, N, NR, O and S;

R is selected from the group consisting of hydrogen, C_{0-3}alkyl, halo, C_{0-3}alkylOR^5, C_{0-3}alkylNR^{5}R^6, C_{0-3}alkyl(CO)OR^5, C_{0-3}alkylNR^{5}R^6 and C_{0-3}alkylaryl;

R^2 is selected from the group consisting of hydrogen, hydroxy, oxo, =NR^6, =NOR^6, C_{1-4}alkylhalo, halo, C_{1-4}alkyl, OC$_{1-4}$alkyl, O(CO)C_{1-4}alkyl, C_{1-4}alkyl(SO)C_{0-4}alkyl, C_{1-4}alkyl(SO$_2$)C_{0-4}alkyl, (SO)C_{0-4}alkyl, (SO$_2$)C_{0-4}alkyl, OC$_{1-4}$alkyl, C_{0-4}alkylcyano, C_{1-4}alkylOR^6 and C_{0-4}alkylNR^{6}R^7;

M^2 is selected from the group consisting of a bond, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{0-4}alkyl(CO)C_{0-4}alkyl, C_{0-3}alkylOC$_{0-3}$alkyl, C_{0-3}alkylNR^{6}C$_{1-3}$alkyl, C_{0-3}alkyl(CO)NR^6, C_{0-4}alkylNR^{6}R^7, C_{0-3}alkylSC$_{0-3}$alkyl, C_{0-3}alkyl(SO)C_{0-3}alkyl and C_{0-3}alkyl(SO$_2$)C_{0-3}alkyl;

R^3 is selected from the group consisting of hydrogen, hydroxy, oxo, =NR^6, =NOR^6, C_{1-4}alkylhalo, halo, C_{1-4}alkyl, OC$_{1-4}$alkyl, O(CO)C_{1-4}alkyl, C_{1-4}alkyl(SO)C_{0-4}alkyl, C_{1-4}alkyl(SO$_2$)C_{0-4}alkyl, (SO)C_{0-4}alkyl, (SO$_2$)C_{0-4}alkyl, C_{0-4}alkylcyano, C_{1-4}alkylOR^6 and C_{0-4}alkylNR^{6}R^7;

X^4 is selected from C, CR or N;

X^5 is selected from C, CR or N;

Q is a 4- to 8-membered ring or bicycle containing one or more atoms independently selected from C, N, O or S, wherein said ring or bicycle may be fused with a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S and wherein the fused ring may be substituted by one or more A;

R^4 is selected from the group consisting of hydrogen, hydroxy, halo, nitro, oxo, C_{1-6}alkylhalo, C_{1-6}alkyl, OC$_{1-6}$alkyl, C_{0-6}alkylC$_{3-6}$cycloalkyl, C_{0-6}alkylaryl, OC$_{0-6}$alkylaryl, (CO)R^6, O(CO)R^6, C_{1-6}alkylOR^6, OC$_{2-6}$alkylOR^6, C_{1-6}alkyl(CO)R^6, OC$_{1-6}$alkyl(CO)R^6, C_{0-6}alkylCO$_2$R^6, OC$_{1-6}$alkylCO$_2$R^6, C_{0-6}alkylcyano, OC$_{1-6}$alkylcyano, C_{0-6}alkylNR^{6}R^7, OC$_{2-6}$alkylNR^{6}R^7, C_{0-6}alkyl(CO)NR^{6}R^7, OC$_{0-6}$alkyl(CO)NR^{6}R^7, C_{0-6}alkylNR^6(CO)R^7, OC$_{2-6}$alkylNR^6(CO)R^7, C_{0-6}alkylNR^6(CO)NR^{6}R^7, C_{0-6}alkylSR^6, OC$_{2-6}$alkylSR^6, C_{0-}

$_{6}$alkyl(SO)R^6, OC_{2-6}alkyl(SO)R^6, C_{0-6}alkylSO_2R^6, OC_{0-6}alkylSO_2R^6, C_{0-6}alkyl$(SO_2)NR^6R^7$, OC_{0-6}alkyl$(SO_2)NR^6R^7$, C_{0-6}alkyl$NR^6(SO_2)R^7$, OC_{2-6}alkyl$NR^6(SO_2)R^7$, NR^6OR^7, $NR^6(CO)OR^7$, SO_3R^6 and a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S, wherein said ring may be substituted by one or more A;

R^5 is selected from the group consisting of hydrogen, hydroxy, halo, oxo, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, OC_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, OC_{0-6}alkylaryl, $(CO)R^6$, $O(CO)R^6$, $O(CO)OR^6$, $(CO)OR^6$, C_{1-6}alkylOR^6, OC_{2-6}alkylOR^6, C_{1-6}alkyl$(CO)R^6$, OC_{1-6}alkyl$(CO)R^6$, C_{0-6}alkylCO_2R^6, OC_{1-6}alkylCO_2R^6, C_{0-6}alkylcyano, OC_{0-6}alkylcyano, C_{0-6}alkylNR^6R^7, OC_{2-6}alkylNR^6R^7, C_{1-6}alkyl$(CO)NR^6R^7$, C_{0-6}alkyl(CO)heteroaryl, C_{0-6}alkyl(CO)aryl, OC_{1-6}alkyl$(CO)NR^6R^7$, C_{1-6}alkyl$(CO)NR^6R^7$, C_{0-6}alkyl$NR^6(CO)R^7$, OC_{2-6}alkyl$NR^6(CO)R^7$, C_{0-6}alkyl$NR^6(CO)NR^6R^7$, C_{1-6}alkyl$NR^6(CO)OR^7$ C_{0-6}alkylSR^6, OC_{2-6}alkylSR^6, C_{0-6}alkyl$(SO)R^6$, OC_{1-6}alkyl$(SO)R^6$, C_{0-6}alkylSO_2R^6, OC_{0-6}alkylSO_2R^6, C_{0-6}alkyl$(SO_2)NR^6R^7$, OC_{0-6}alkyl$(SO_2)NR^6R^7$,C_{0-6}alkyl$NR^6(SO_2)R^7$, OC_{2-6}alkyl$NR^6(SO_2)R^7$, C_{0-6}alkyl$NR^6(SO_2)NR^6R^7$, OC_{2-6}alkyl$NR^6(SO_2)NR^6R^7$, $(CO)NR^6R^7$, $O(CO)NR^6R^7$, NR^6OR^7, $NR^6(CO)OR^7$, SO_3R^6 and a 5 -or 6-membered ring containing one or more atoms independently selected from C, N, O or S, wherein said ring may be substituted by one or more A;

R^6 and $R^7$are independently selected from hydrogen, C_{1-6}alkyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{1-6}alkylheteroaryl and a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S, and wherein R^6 and R^7 may together form a 5- or 6-membered ring containing one or more atoms independently selected from C, N, O or S;

wherein any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl and C_{0-6}alkylheteroaryl defined under R^1, R^2, R^3, R^4, R^5, R^6 and R^7 may be substituted by one or more A;

A is selected from the group consisting of hydrogen, hydroxy, oxo, halo, nitro, C_{1-6}alkylhalo, OC_{1-6}alkylhalo, C_{1-6}alkyl, C_{0-4}alkylC_{3-6}cycloalkyl, C_{2-6}alkenyl, OC_{1-6}alkyl, C_{0-3}alkylaryl, C_{1-6}alkylOR^6, OC_{2-6}alkylOR^6, C_{1-6}alkylSR^6, OC_{2-6}alkylSR^6, $(CO)R^6$, $O(CO)R^6$, OC_{2-6}alkylcyano, C_{0-6}alkylcyano, C_{0-6}alkylCO_2R^6, OC_{1-6}alkylCO_2R^6, $O(CO)OR^6$, OC_{1-6}alkyl$(CO)R^6$, C_{1-6}alkyl$(CO)R^6$, NR^6OR^7, C_{0-6}alkylNR^6R^7, OC_{2-6}alkylNR^6R^7, C_{0-6}alkyl$(CO)NR^6R^7$, OC_{1-6}alkyl$(CO)NR^6R^7$, OC_{2-6}alkyl$NR^6(CO)R^7$, C_{0-6}alkyl$NR^6(CO)R^7$, C_{0-6}alkyl$NR^6(CO)NR^6R^7$, $O(CO)NR^6R^7$, $NR^6(CO)OR^7$, C_{0-6}alkyl$(SO_2)NR^6R^7$, OC_{2-6}alkyl$(SO_2)NR^6R^7$, C_{0-6}alkyl$NR^6(SO_2)R^7$, OC_{2-}

$_{6}$alkylNR^{6}(SO$_2$)R^{7}, SO$_3$R^{6}, C$_{1\text{-}6}$alkylNR^{6}(SO$_2$)NR^{6}R^{7}, OC$_{2\text{-}6}$alkyl(SO$_2$)R^{6}, C$_{0\text{-}6}$alkyl(SO$_2$)R^{6}, C$_{0\text{-}6}$alkyl(SO)R^{6} and OC$_{2\text{-}6}$alkyl(SO)R^{6};

m and p are independently selected from the group consisting of 0, 1, 2, 3 and 4;

n, o and q are each independently selected from 0, 1, 2 or 3;

or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such inhibition.

12. A method for the treatment of gastro-esophageal reflux disease (GERD), whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I as defined in claim 11, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such treatment.

13. A method for the prevention of reflux, whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I as defined in claim 11, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such prevention.

14. A method for the treatment of, or prevention of, regurgitation, whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I as defined in claim 11, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such treatment or prevention.

15. A method for the prevention of, or treatment of, lung disease, whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I as defined in claim 11, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such treatment or prevention.

16. A method for managing failure to thrive, whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I as defined in claim 11, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such management.

17. A method for treatment or prevention of asthma, whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I as defined in claim 11,

or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such treatment or prevention.

18. A method according to claim 17, wherein the asthma is reflux-related asthma.

19. A method for treatment or prevention of laryngitis, whereby a pharmaceutically and pharmacologically effective amount of a compound of formula I as defined in claim 11, or a pharmaceutically acceptable salt or an optical isomer thereof, is administered to a subject in need of such treatment or prevention.

20. A method according to any one of claims 11-19, wherein the compound of formula I is selected from the group of compounds consisting of 4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester hydrochloride,
4-[5-(3-Methoxyphenyl)-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester hydrochloride,
4-[5-(3-Trifluoromethyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(3-Cyano-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester),
4-[5-(3-Fluoro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(3-Iodo-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(3-Trifluoromethoxy-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-[5-(3-Bromo-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,
4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid methyl ester,
4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid propyl ester,
4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid butyl ester,
4-[5-(3-Methoxy-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-2-methyl-piperazine-1-carboxylic acid ethyl ester,
4-(5-m-Tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid isopropyl ester,

4-[1-(5-(3-Methyl-phenyl)-[1,2,4]oxadiazol-3-yl)-ethyl]-piperazine-carboxylic acid ethyl ester or

4-[5-(3-Furan-3-yl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{Cyano-[5-(2-fluoro-5-methyl-phenyl)-isoxazol-3-yl]-methyl}-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-2-oxo-piperazine-1-carboxylic acid ethyl ester,

4-[1-(5-m-Tolyl-[1,2,4]oxadiazol-3-yl)-ethyl]-piperazine-1-carboxylic acid ethyl-methyl-amide,

(R)-and (S)-4-[1-(5-(3-Methyl-phenyl)-[1,2,4]oxadiazol-3-yl)-ethyl]-piperazine-carboxylic acid ethyl ester,

(R)-and (S)-4-[1-(5-(3-Methyl-phenyl)-[1,2,4]oxadiazol-3-yl)-ethyl]-piperazine-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-propyl}-piperazine-1-carboxylic acid ethyl ester,

(S)-4-{1-[5-(5-Chloro-2-fluoro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

(S)-{1-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

(S)-4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

(R)-4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-2-methyl-piperazine-1-carboxylic acid ethyl ester,

(S)- 4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-2-methyl-piperazine-1-carboxylic acid ethyl ester,

(R)-3-Methyl-4-(5-m-tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester,

(S)-3-Methyl-4-(5-m-tolyl-[1,2,4]oxadiazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester, 4-[5-(3-Methylsulfanyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Chloro-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-yl-(R)-methyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-yl-(S)-methyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Bromo-2-fluoro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2,5-Dichloro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-(5-Thiophen-3-yl-isoxazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

(R)- and (S)-4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester enantiomers,

4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-propyl}-piperazine-1-carboxylic acid ethyl ester,

4-{Cyclopropyl-[5-(2-fluoro-5-methyl-phenyl)-isoxazol-3-yl]-methyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-ethyl}-3-(*R*)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)

4-{1-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-yl]-ethyl}-3-(*S*)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)

4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-3-(*R*)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)

4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-3-(*S*)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)

4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-2-(R)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)

4-{1-[5-(3-Chloro-phenyl)-isoxazol-3-yl]-ethyl}-2-(S)-methyl-piperazine-1-carboxylic acid ethyl ester, (2 diastereomers)

(*R*)-4-[5-(3-Chloro-phenyl)-isoxazol-3-ylmethyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,

(*R*)-4-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-ylmethyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,

(*S*)-4-[5-(3-Chloro-phenyl)-isoxazol-3-ylmethyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,

(*S*)-4-[5-(2-Fluoro-5-methyl-phenyl)-isoxazol-3-ylmethyl]-3-methyl-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Chloro-phenyl)-oxazol-2-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Chloro-2-fluoro-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Chloro-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-3-(*S*)-methyl-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-3-(*R*)-methyl-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Chloro-phenyl)-[1,2,4]oxadiazol-3-yl]-ethyl}-3-(*R*)-methyl-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Chloro-2-fluoro-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(5-Chloro-2-fluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-methyl-phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(2-Fluoro-5-methyl-phenyl)-[1,3,4]oxadiazol-2-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-(5-m-Tolyl-isoxazol-3-ylmethyl)-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-methoxy-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-cyano-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(3-Formyl-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Cyano-2-fluoro-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(5-Chloro-2-fluoro-phenyl)-isoxazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(5-Chloro-2-fluoro-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-[1-(5-m-Tolyl-isoxazol-3-yl)-ethyl]-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Methoxy-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(3-Cyano-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(5-Cyano-2-fluoro-phenyl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-{1-[5-(2-Methyl-pyridin-4-yl)-isoxazol-3-yl]-ethyl}-piperazine-1-carboxylic acid ethyl ester,

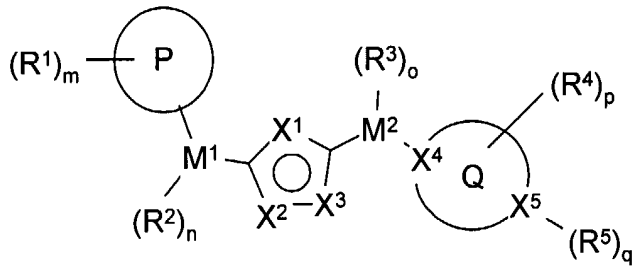
4-{1-[5-(5-Chloro-2-fluoro-phenyl)-isoxazol-3-yl]-2,2,2-trifluoro-ethyl}-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Fluoro-5-iodo-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester,

4-[5-(2-Hydroxy-5-methyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester, 4-[5-(5-Chloro-2-hydroxy-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazine-1-carboxylic acid ethyl ester or a pharmaceutically acceptable salt or an optical isomer thereof.

Abstract

The present invention relates to the use of a compound of formula I for the inhibition of transient lower esophageal sphincter relaxations. A further aspect of the invention is directed to the use of compounds of formula I for the treatment of gastro-esophageal reflux disease.



(I) (I)